FAST TRACK ARTICLE

Analysis of Adverse Events after Anthrax Immunization in US Army Medical Personnel

Glenn M. Wasserman, MD, MPH
John D. Grabenstein, PhD
Phillip R. Pittman, MD, MPH
Mark V. Rubertone, MD, MPH
Paul P. Gibbs, MPH
Linda Z. Wang, MS
Lance G. Golder, MPA

A broad range of health effects in a cohort of 601 health care personnel, immunized with anthrax vaccine adsorbed (AVA) as a military occupational health requirement, were assessed to evaluate adverse events both qualitatively and quantitatively. Active surveillance showed that localized reactions were common and occurred more often in women than men. Five patients were reported to the Vaccine Adverse Event Reporting System, but only one event could be definitively attributed to immunization, a large localized reaction. Two separate cohort studies, one using nested data from a standardized health risk appraisal instrument and the other comparing rates of outpatient visits and hospitalizations, did not reveal significant differences between AVA-immunized and unimmunized individuals. Our findings suggest that AVA is relatively reactogenic but do not indicate serious adverse health effects due to immunization. (J Occup Environ Med. *2003; 45:222–233*)

U. S. State Department and Department of Defense (DOD) intelligence documents and reports indicate that future deployment of biological agents by foreign militaries or terrorists is likely.[1–5] These agents are relatively inexpensive, are easy to mass produce, are easily weaponized, stay active over many years, and can be dispersed by wind over vast areas. At least 12 nations have acquired or are trying to acquire biological weapons.[6,7] The former Soviet Union stored more than 30 metric tons of *Bacillus anthracis* spores in some of their 52 bioweapons program sites. Their effectiveness was demonstrated during an unintentional release of a cloud of anthrax spores at Sverdlovsk in 1979. At least 68 citizens died downwind from the site.[3,5,8] Iraq also produced weapons containing biological and chemical agents, including at least 42 tons of concentrated anthrax spores. At the end of 1990, according to Iraqi statements, 25 SCUD/Al-Hussain missiles, each carrying 145 L of agent, were ready for use. Aircraft aerosolized spraying and R400 bombs were also available.[2,5,9] In the United States, anthrax spores distributed in the mail led to 12 confirmed or suspected cases of cutaneous anthrax and 11 confirmed cases of inhalational anthrax, five fatal, in late 2001.[10] Because of the known threat, the DOD initiated a program to immunize military personnel as an occupational health requirement under DOD's Force Health Protection Program.[4]

Anthrax vaccine adsorbed (AVA), licensed by the Food and Drug Administration (FDA) in 1970, was determined to be safe and effective in

From the Preventive Medicine Department, Tripler Army Medical Center, Honolulu, Hawaii (Dr Wasserman); Anthrax Vaccine Immunization Program Agency, Falls Church, VA (Dr Grabenstein); Anthrax Vaccine Clinical Research Studies, US Army Medical Research Institute of Infectious Diseases, Frederick, MD (Dr Pittman); Army Medical Surveillance Activity, US Army Center for Health Promotion and Preventive Medicine, Silver Spring, MD (Dr Rubertone); Chief Biostatistician, Anthrax Vaccine Clinical Research Studies, US Army Medical Research Institute of Infectious Diseases, Frederick, MD (Mr Gibbs); Naval Health Research Center, San Diego, CA (Ms Wang); and Pacific Regional Medical Command, Anthrax Vaccine Immunization Program, Honolulu, Hawaii (Mr Golder).

The views expressed in this manuscript are those of the authors and do not reflect official policy or position of the Department of the Army, Department of Defense or the U.S. Government.

Address correspondence to Glenn Wasserman, Preventive Medicine Department, Tripler Army Medical Center, U.S. Army, Honolulu, HI 96859-5000; *E-mail*: glenn.wasserman@amedd.army.mil

DOI: 10.1097/01.jom.0000058345.05741.6b

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
MAR 2003		**00-00-2003 to 00-00-2003**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Analysis of Adverse Events after Anthrax Immunization in US Army Medical Personnel	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Tripler Army Medical Center,Preventive Medicine Department,Honolulu,HI,96859-5000**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**	**Same as Report (SAR)**	**12**	

studies at wool mills, where this disease had been an occupational hazard.[11–13] Postmarketing surveillance and the Vaccine Adverse Event Reporting System (VAERS) did not demonstrate either a significant trend or any unusual character of potentially serious side effects after licensure.[13–16] Anecdotal comments by service members who received this vaccine in 1998, however, under the DOD's Anthrax Vaccine Immunization Program (AVIP), suggested that perceived side effects might be more frequent or more severe than had been reported in previous studies.[17] We performed this study to actively survey adverse events in a defined medical staff cohort who were to be immunized in the context of routine military occupational medicine requirements.

Methods

Health care personnel stationed at Tripler Army Medical Center (TAMC) and at Schofield Barracks Health Clinic, 15 miles away, who started the anthrax vaccine series between September 12 and October 16, 1998, were enrolled in the project. TAMC is a 229-bed tertiary care hospital and ambulatory care center in Honolulu, Hawaii. Schofield Barracks Health Clinic is TAMC's largest primary care clinic, serving soldiers and families in the 25th Infantry Division. All individuals traveling to or potentially deploying to countries determined by DOD's operational risk assessment for exposure to weaponized anthrax were immunized according to standard DOD policy. The dates of enrollment corresponded with the immunization of soldiers in the Korea Medical Augmentee Program, individuals who would deploy to Korea if war recurred.

All were immunized with AVA (BioPort Corporation, Lansing, MI) in accordance with DOD AVIP requirements and procedures. The only additional requirement was for the individual to complete a survey 1 to 2 weeks, or as close thereafter, after immunization. There were no individuals who requested not to be vaccinated. Strict patient confidentiality was maintained in administering, storing, and analyzing all surveys.

Vaccinees registered at the immunization clinic, were offered information regarding the anthrax vaccine, and were interviewed to determine if they had contraindications to immunization. Individuals were excluded from immunization if they had an active infection or acute illness, were pregnant, were receiving immunosuppressive drugs, or had a serious adverse reaction to a previous anthrax vaccine.[18,19] Those who were medically cleared were immunized.

Participants were immunized according to the FDA-approved, AVA dosage schedule that stipulates subcutaneous administration of the vaccine at 0, 2, and 4 weeks and at 6, 12, and 18 months.[18,19] Records of the immunization, including date, person authorizing immunization, and lot number, were recorded in the US Army's centralized Medical Occupational Data System according to standard DOD AVIP procedures to assure that the correct number and proper timing of subsequent doses occurred. Records were also stored in the automated Composite Health Care System that records immunization and other patient-oriented data at TAMC.[16]

The survey of reported events after AVA immunization was approved by the Human Use Committee of the US Army Medical Research Institute of Infectious Diseases. Approval for the overall project, including the cohort comparison of reported health and wellness using a health risk appraisal instrument, and the cohort comparison of outpatient health visits and hospitalizations, was granted by the TAMC Department of Clinical Investigation. All procedures were conducted under federal rules for protection of research subjects[20] and were without increased risks to the study subjects.

Survey of Symptoms, Severity, and Duration After Immunization

Individuals completed a survey at least 1 week, and most often 2 weeks, after immunization. The survey instrument was adapted from a US Army Medical Research Institute of Infectious Diseases occupational health clinic template used to assess events after immunization. The survey asked explicitly about loss of appetite, headache, fatigue, muscle aches, joint aches, itching, nausea and/or vomiting, diarrhea, chills, shortness of breath, and fever. Individuals indicated severity using a symptom severity key: "none," "symptoms and signs can be ignored," "symptoms and signs affect activity but can perform anyway," "symptoms and signs affect activity, but relieved by medication," and "symptoms and signs not relieved by medication, can't perform activities." If they had any symptoms, they listed the duration, using a duration key: "less than 6 hours," "7–24 hours," "25–72 hours," or "greater than 72 hours." Additional space was provided for individuals to list other symptoms and provide comments. At the same time, using a sign-in roster, we requested information whether they had an outpatient medical visit, were hospitalized, or missed one or more 8-hour shifts of work.

After the first three immunizations, additional data were collected on localized, injection-site reactions using an additional survey questionnaire. Consequently, personnel reported these additional localized events retrospectively for the first three inoculations, approximately 6 months after the study began (ie, when they came in for their fourth immunization), and prospectively thereafter. This survey included diameter of erythema, tenderness, itching at site, swelling below the elbow, and "presence of a lump or knot." We assessed severity of symptoms using a key identical to that of the original survey instrument.

Data were analyzed using Statistical Analysis Systems (SAS) software (SAS Institute, Cary, NC). Univariate analysis and logistic regression were performed to determine the association of reported symptoms with demographic characteristics. Statistical significance was designated at $P < 0.05$ (two tailed) and 95% confidence intervals.

Vaccine Adverse Event Reporting System Reports

In accordance with DOD's guidance on reporting VAERS, any individual who was hospitalized, had more than one lost duty day (24 h or more) after anthrax immunization, or had an event suspected to have resulted from contamination of a vaccine lot was evaluated further. Medical records of these individuals were obtained, contact was made with their medical provider, and/or information was obtained directly from the patient to document the clinical details related to the event. Except for events determined by a physician to be unrelated to immunization, the event was reported to the VAERS program, operated jointly by the FDA and the Centers for Disease Control and Prevention.[21] Also, healthcare providers were instructed and encouraged to complete VAERS reports if in their professional judgment any event after anthrax immunization was unexpected in nature or severity. In addition, individuals who were immunized could also self-report directly to VAERS.

Self-Reported Health and Wellness at Completion of the Vaccine Series

Soldiers stationed at TAMC were scheduled to complete the Health Enrollment Assessment Review Survey (HEARS), Version 2.1 between May 1 and August 31, 2000. This survey is a standardized, validated health risk appraisal tool that the DOD uses to provide health risk information and feedback for health care beneficiaries and population-based health assessments for health care planners.[22,23] Results of the survey are also provided to the individual's primary care provider. Soldiers completed this survey privately using a computer located at TAMC's Health Education and Promotion Center or Schofield Barrack's Community Health Clinic. Trained, community health nurses provided health promotion-related feedback in a confidential manner. No reference to the anthrax vaccine was made either orally or in written form during the survey.

The HEARS contains demographic information provided by the respondent regarding gender, marital status, highest educational level completed, annual total family income, and total number of children at home. Questions regarding reported aspects of health and wellness were selected from this 156-question survey based on their relevance to this project. These questions included self-reported general health; ever diagnosed with "chronic headaches," "neurologic disease," "asthma," "muscle, joint or back problems," and "depression"; self-reported mental health; experiencing survey-defined levels of stress during the past 12 months; seeing a mental health professional during the past 12 months; experiencing serious personal or emotional problems during the past 12 months; feeling down, depressed or hopeless; bothered by little interest or pleasure in doing things; and satisfaction with life.

HEARS data from soldiers in the TAMC cohort immunized beginning in September 1998 were compared with data from anthrax-unvaccinated soldiers who also were at TAMC in September 1998. This was determined by linking Social Security numbers (SSNs) for the individuals who completed HEARS surveys to the Defense Medical Surveillance System (DMSS) database. DMSS provides a longitudinal record of demographic characteristics, periods of service, locations of assignment, medical events, and anthrax immunization records for all members of the active component of the US military.[24] DMSS is maintained by the Army Medical Surveillance Activity (AMSA), US Army Center for Health Promotion and Preventive Medicine, Washington, DC. SSNs were used for matching, then promptly deleted. Between May 1, 2000 and August 31, 2000, 3234 soldiers completed the HEARS survey. Three hundred and one soldiers belonged to the TAMC 601 cohort and 639 were in the unimmunized control group of soldiers stationed at TAMC in September 1998 who never received an anthrax immunization. Data analysis was performed at the Naval Health Research Center in San Diego, CA, to assure that, even without names, individuals could not be identified based on their responses, thus assuring strict confidentiality.

Data were analyzed using SAS statistical software. Univariate analysis using Chi-square (95% confidence interval, two-tailed) was performed to define cohort differences with regards to demographic characteristics and to compare responses between cohorts. Stratification was used to adjust for demographic differences between the groups.

Cohort Study of Outpatient Health Care Visits and Hospitalizations

The DMSS identified active duty soldiers stationed at TAMC on October 1, 1998. Outpatient visits and hospitalizations in the military health care system in this group from October 1, 1998, through September 30, 2000, were evaluated. Up to eight outpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes and up to four inpatient ICD-9-CM codes are recorded by the DMSS.

Three groups were identified: 1) 600 soldiers enrolled in the TAMC survey cohort; 2) 225 soldiers who received an anthrax immunization

TABLE 1
TAMC 601 Cohort: Distribution by Age, Gender and Rank

	No.	Percent	Age Distribution of Survey Population			
			Median (yrs)	Mean (yrs)	St. Dev.	Range (yrs)**
All*	601	100.0%	28	29.9	7.5	17–28
Males	416	69.2%	29	30.3	7.4	17–61
Females	185	30.8%	27	29.0	7.5	17–53
Military rank						
E1–E4	203	33.8%	24	23.9	3.7	17–37
E5–E9	222	36.9%	31	31.1	5.2	20–49
O1–O3	101	16.8%	30	31.5	6.7	18–52
O4–O8	74	12.3%	39	41.0	6.5	32–61

* Includes one deployable Department of the Army civilian.
** Range is mean age over entire survey period.

outside the enrollment period; and 3) 637 soldiers who were not immunized with anthrax vaccine before October 1, 2000, the cutoff date for this study. These groups were then categorized into "pre-immunization" and "post-immunization" person-time groupings for analysis. The pre-immunization period consisted of the entire 2-year period in group 3 individuals and the period for individuals in group 2 preceding the date of their first anthrax immunization. Person–time data for the post-immunization period consisted of the entire 2-year period in individuals in group 1, and the period for individuals in group 2, up to the date of their first anthrax immunization. AMSA linked SSNs of the individuals in the TAMC survey cohort with the DMSS database. Rate ratios were used to compare overall rates of ambulatory visits and hospitalizations, as well as ICD-9-CM–based diagnostic groups, between the pre- and post-immunization periods. Specific categories of interest were musculoskeletal (ICD-9-CM codes 710–739), mental (290–319), digestive (520–579), injury (800–999), and symptoms ill defined (780–799). Rate ratios were adjusted for age and gender by Poisson regression modeling using SAS' Genmod procedure.[25] Strict confidentiality of medical information and records was maintained in accordance with standard AMSA procedures.

Results

600 soldiers and one Department of the Army civilian worker began the anthrax vaccine series between September 12 and October 13, 1998 at TAMC. The composition of the TAMC 601 cohort, characterized by gender, rank, and age is shown in Table 1.

Survey of Symptoms, Severity, and Duration After Immunization

Immunizations (n = 3069) were administered to this cohort at TAMC. Of these, 2849 questionnaires (93%; Table 2) and 2734 surveys (89%) for local reactions (Table 3) were completed. Survey completion rates, defined as the number of surveys completed divided by 601 individuals, for questionnaires 1 and 2 are shown in Fig. 1. During the 2-year survey period, enrollees dropped out because of pregnancy, medical exemptions, leaving the Army, and performing duty elsewhere. Some of these were temporary, for example, pregnancy, certain medical exemptions, and temporary duty elsewhere. Many individuals were transferred to other assignments, as a tour of duty outside the contiguous United States is generally 3 years. These individuals continued to receive the anthrax vaccine at their new location, but their surveys were not collected at TAMC. Others retired, completed their military obligation, entered the reserves, or were discharged within the 2-year survey period. Consequently, 48% of the cohort completed the sixth survey. Of 3060 immunizations administered at TAMC, the most common reported post-immunization events from questionnaire 1, in order of decreasing frequency, were muscle ache, fatigue, headache, and joint ache (Table 2). Women in general had slightly higher rates for these reported events than men. The median duration for these reported events was 24 to 72 hours, with no distinct difference by gender.

Reported localized events assessed in questionnaire 2 were common (Table 3). The presence of a "lump or knot" was most often reported after immunization, followed by localized muscle soreness, localized itching, and erythema greater than 5 cm in diameter. The rates of reported muscle soreness decreased during the first five immunizations before slightly increasing with the sixth dose. The rates of the other reported localized events were similar after each immunization. 6% of patients reported pain limiting motion of the elbow and swelling of the lower arm.

Gender was significantly correlated with reported localized events. The rate ratio for women compared to men for report of any local reaction was 1.4 (95% confidence interval: 1.3–1.5). Rate ratios were highest for reported localized pruritus (RR: 2.3; 95% CI: 2.1–2.5), followed

TABLE 2
Incidence of Reported Events in TAMC 601 Cohort: Questionnaire #1

Symptom	Severity	Frequency		Percent (95% Confidence Interval)	
		Male	Female	Male	Female
Muscle ache	No symptoms	1177	446	58.7 (56.5, 60.9)	52.7 (49.4, 56.2)
	Symptoms can be ignored	338	134	16.9 (15.2, 18.5)	15.9 (13.3, 18.4)
	Symptoms affect activity but can still perform	316	140	15.8 (14.1, 17.4)	16.6 (14.0, 19.1)
	Symptoms affect activity, relieved by medication	130	102	6.5 (5.4, 7.6)	12.1 (9.8, 14.3)
	Symptoms not relieved by medication, cannot perform	43	23	2.2 (1.5, 2.8)	2.7 (1.6, 3.8)
Fatigue	No symptoms	1574	537	78.5 (76.7, 80.2)	63.6 (60.4, 66.9)
	Symptoms can be ignored	159	86	7.9 (6.7, 8.1)	10.2 (9.1, 12.3)
	Symptoms affect activity but can still perform	182	139	9.1 (7.8, 13.9)	16.5 (10.4, 19.0)
	Symptoms affect activity, relieved by medication	65	66	3.2 (2.5, 6.0)	7.8 (4.0, 9.7)
	Symptoms not relieved by medication, cannot perform	24	17	1.2 (0.7, 1.1)	2.0 (1.7, 3.0)
Headache	No symptoms	1662	570	82.9 (81.3, 84.6)	67.5 (64.2, 70.7)
	Symptoms can be ignored	137	69	6.8 (5.7, 8.0)	8.2 (6.3, 10.1)
	Symptoms affect activity but can still perform	106	89	5.3 (4.3, 6.3)	10.5 (8.4, 12.6)
	Symptoms affect activity, relieved by medication	71	96	3.5 (2.7, 4.4)	11.4 (9.2, 13.5)
	Symptoms not relieved by medication, cannot perform	28	21	1.4 (0.9, 1.9)	2.5 (1.4, 3.6)
Joint ache	No symptoms	1677	656	83.7 (82.0, 85.3)	77.6 (74.8, 80.5)
	Symptoms can be ignored	119	51	5.9 (4.9, 7.0)	6.0 (4.4, 7.7)
	Symptoms affect activity but can still perform	115	70	5.7 (4.7, 6.8)	8.3 (6.4, 10.2)
	Symptoms affect activity, relieved by medication	65	56	3.2 (2.5, 4.0)	6.6 (4.9, 8.3)
	Symptoms not relieved by medication, cannot perform	28	12	1.4 (0.9, 1.9)	1.4 (0.6, 2.2)
Loss of appetite	No symptoms	1876	718	93.6 (92.5, 94.7)	85.0 (82.5, 87.4)
	Symptoms can be ignored	74	56	3.7 (2.9, 4.5)	6.6 (4.9, 8.3)
	Symptoms affect activity but can still perform	36	46	1.8 (1.2, 2.4)	5.4 (3.9, 7.0)
	Symptoms affect activity, relieved by medication	15	21	0.8 (0.4, 1.1)	2.5 (1.4, 3.6)
	Symptoms not relieved by medication, cannot perform	3	4	0.2 (0.0, 0.3)	0.5 (0.0, 1.0)
Nausea and vomiting	No symptoms	1896	727	94.6 (93.6, 95.6)	86.0 (83.7, 88.4)
	Symptoms can be ignored	48	38	2.4 (1.7, 3.1)	4.5 (3.1, 5.9)
	Symptoms affect activity but can still perform	35	41	1.8 (1.2, 2.4)	4.9 (3.4, 6.3)
	Symptoms affect activity, relieved by medication	12	27	0.6 (0.3, 0.9)	3.2 (2.0, 4.4)
	Symptoms not relieved by medication, cannot perform	12	12	0.6 (0.3, 0.9)	1.4 (0.6, 2.2)
Fever	No symptoms	1916	766	95.6 (94.7, 96.5)	90.7 (88.7, 92.7)
	Symptoms can be ignored	44	11	2.2 (1.5, 2.9)	1.3 (0.5, 2.1)
	Symptoms affect activity but can still perform	20	28	1.0 (0.6, 1.4)	3.3 (2.1, 4.6)
	Symptoms affect activity, relieved by medication	21	38	1.1 (0.6, 1.5)	4.5 (3.1, 5.9)
	Symptoms not relieved by medication, cannot perform	3	2	0.2 (0.0, 0.3)	0.2 (0.1, 0.6)
Itching over entire body	No symptoms	1914	756	95.5 (94.6, 96.4)	89.5 (87.4, 91.6)
	Symptoms can be ignored	41	30	2.1 (1.4, 2.7)	3.6 (2.3, 4.8)
	Symptoms affect activity but can still perform	32	29	1.6 (1.0, 2.2)	3.4 (2.2, 4.7)
	Symptoms affect activity, relieved by medication	8	25	0.4 (0.1, 0.7)	3.0 (1.8, 4.1)
	Symptoms not relieved by medication, cannot perform	9	5	0.5 (0.2, 0.8)	0.6 (0.1, 1.1)
Chills	No symptoms	1911	768	95.4 (94.4, 96.3)	90.9 (88.9, 92.9)
	Symptoms can be ignored	35	22	1.8 (1.2, 2.3)	2.6 (1.5, 3.7)
	Symptoms affect activity but can still perform	37	27	1.9 (1.2, 2.5)	3.2 (2.0, 4.4)
	Symptoms affect activity, relieved by medication	16	21	0.8 (0.4, 1.2)	2.5 (1.4, 3.6)
	Symptoms not relieved by medication, cannot perform	5	7	0.3 (0.0, 0.5)	0.8 (0.2, 1.5)
Diarrhea	No symptoms	1928	803	96.2 (95.4, 97.1)	95.0 (93.5, 96.5)
	Symptoms can be ignored	33	7	1.7 (1.1, 2.2)	0.8 (0.2, 1.5)
	Symptoms affect activity but can still perform	22	14	1.1 (0.6, 1.6)	1.7 (0.8, 2.5)
	Symptoms affect activity, relieved by medication	15	14	0.8 (0.4, 1.1)	1.7 (0.8, 2.5)
	Symptoms not relieved by medication, cannot perform	6	7	0.3 (0.1, 0.5)	0.8 (0.2, 1.5)
Shortness of breath	No symptoms	1947	805	97.2 (96.4, 97.9)	95.3 (93.8, 96.7)
	Symptoms can be ignored	23	9	1.2 (0.7, 1.6)	1.1 (0.4, 1.8)
	Symptoms affect activity but can still perform	20	18	1.0 (0.6, 1.4)	2.1 (1.1, 3.1)
	Symptoms affect activity, relieved by medication	8	11	0.4 (0.1, 0.7)	1.3 (0.5, 2.1)
	Symptoms not relieved by medication, cannot perform	6	2	0.3 (0.1, 0.5)	0.2 (0.1, 0.6)

TABLE 3
Incidence of Reported Local Events in TAMC 601 Cohort: Questionnaire #2

Symptom	# 1	# 2	# 3	# 4	# 5	# 6
Lump or "knot"						
Male	63.9%	63.9%	59.8%	65.2%	55.6%	59.0%
Female	90.5%	87.3%	81.0%	92.8%	83.2%	89.0%
Muscle soreness						
Male	66.0%	63.3%	61.4%	60.2%	49.8%	52.4%
Female	79.7%	76.6%	69.6%	65.2%	56.1%	61.0%
Localized itching						
Male	25.3%	25.5%	24.2%	27.2%	30.3%	30.5%
Female	61.4%	59.5%	56.3%	68.1%	60.7%	59.8%
Redness >5 cm						
Male	16.6%	18.2%	15.2%	22.8%	21.7%	21.0%
Female	41.1%	41.1%	42.4%	42.0%	37.4%	42.7%
Pain that limits motion of elbow						
Male	9.8%	8.7%	7.6%	7.9%	5.8%	5.2%
Female	17.1%	13.3%	11.4%	10.9%	7.5%	8.5%
Swelling of lower arm						
Male	10.1%	9.5%	9.2%	6.7%	5.8%	9.5%
Female	12.7%	13.3%	12.7%	12.3%	5.6%	11.0%

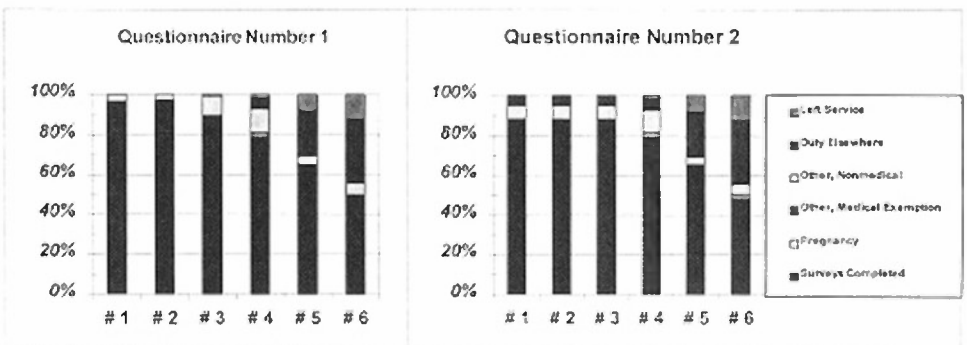


Fig. 1. Survey completion rates for questionnaire 1 and 2 in TAMC 601 cohort

by redness greater than 5 cm in diameter (RR: 2.2; 95% CI: 1.9–2.5), pain limiting motion of elbow (RR: 1.6; 95% CI: 1.2–2.0), lump or knot (RR: 1.42; 95% CI: 1.4–1.5), swelling of the lower arm (RR: 1.4; 95% CI: 1.1–1.7), and muscle soreness (RR: 1.2; 95% CI: 1.1–1.2). Logistic regression analysis using each type of local event as the dependent variable, and gender (F:M), age (<30: ≥30 years), and immunization grouping (doses 4–6: doses 1–3) as independent variables, demonstrated the strongest statistical association between each localized event and gender, with less effect due to age or immunization grouping. That is, the odds ratios in the univariate analysis of localized events associated with gender were unchanged in the final fitted model of the multivariate analysis.

On average, after each immunization, 3.9% of the men and 5.8% of the women reported that they could not perform one or more of their normal duties temporarily because of an event. Muscle aches, followed in frequency by headaches, joint ache, and fatigue again were the most common reported events affecting performance of duties (Table 4). Rates of performance impairment overall were highest after the first immunization (6.0% male, 12.2% female), and decreased during the second immunization with reports primarily of muscle aches and joint aches. Observable trends by immunization dose thereafter were unremarkable.

VAERS Reports

There were five events reported to VAERS from a total of 3069 immunizations administered. The medical information is summarized as follows:

- A 35-year-old male developed myalgias, upper extremity motor weakness, and tremors beginning 4 days after his second immunization. His serum creatinine phosphokinase was above 1000 mg/dL. This condition resolved after treatment with prednisone and has not recurred.

TABLE 4
Incidence of Reported Events in TAMC 601 Cohort members Who Reported They Could Not Perform All Activities

	# 1	# 2	# 3	# 4	# 5	# 6
Any event—male*	6.0%	4.9%	2.7%	2.4%	4.0%	3.4%
Any event—female*	12.2%	5.6%	3.8%	5.1%	1.9%	6.1%
Muscle aches	4.1%	3.1%	1.3%	1.7%	1.0%	1.7%
Fatigue	2.9%	1.4%	0.6%	1.1%	0.8%	1.7%
Headache	3.1%	1.4%	1.3%	1.1%	1.6%	1.7%
Joint aches	2.6%	1.5%	0.9%	1.1%	0.8%	1.0%
Loss of appetite	0.3%	0.3%	0.2%	0.4%	0.0%	0.0%
Nausea or vomiting	1.4%	1.2%	0.6%	0.4%	0.8%	0.3%
Fever	0.2%	0.0%	0.0%	0.4%	0.3%	0.3%
Itching over entire body	0.7%	0.7%	0.4%	0.0%	0.3%	1.0%
Chills	0.9%	0.3%	0.0%	0.5%	0.3%	0.3%
Diarrhea	0.7%	0.7%	0.0%	0.4%	0.5%	0.3%
Shortness of breath	0.5%	0.0%	0.4%	0.2%	0.3%	0.3%

* Individuals with at least one reported event (over 11 possible symptoms counting only once per individual for each immunization).

TABLE 5
HEARS Study: Characterization of the AVA-immunized and Unimmunized TAMC Cohorts

	TAMC 601 Cohort		Unvaccinated Cohort	
	n	Percent	*n*	Percent
Entire cohort	301	100.0%	639	100.0%
Gender				
Male	215	69.1%	368	57.6%
Female	96	30.9%	271	42.4%
Age				
<30	153	49.2%	248	38.8%
30+	158	50.8%	391	61.2%
Marital Status				
Single, never married	46	15.1%	139	21.9%
Married	228	74.8%	432	67.9%
Divorced	31	10.2%	65	10.2%
Education				
High school	163	52.4%	163	25.5%
College	92	29.6%	151	23.6%
Postgraduate	56	18.0%	325	50.9%
Total annual household income				
<$25,000	83	26.8%	113	17.8%
$25,000–$50,000	131	42.3%	196	30.8%
$50,000+	95	31.0%	327	51.4%

- A 32-year-old male with a history of sarcoidosis developed chest pain, dyspnea, arthralgias, myalgias, fever, and chills shortly after his second immunization. This resolved after 3 to 4 days.
- A 38-year-old female developed pruritic swelling encircling her upper arm and most of her forearm after the second immunization. This resolved without intervention.
- A 40-year-old male noted intermittent fasciculations, numbness, and tingling of his right arm in the distribution of the medial cord of the right brachial plexus. His serum creatinine phosphokinase was unremarkable as were his electromyography and nerve conduction velocities. His symptoms began 6 weeks after his third immunization and resolved without intervention.
- A 23-year-old female demonstrated clinical and magnetic resonance imaging findings consistent with an inflammatory demyelination disease approximately 1 week after her fourth immunization. She now has a diagnosis of multiple sclerosis.

Self-Reported Health and Wellness at Completion of the Vaccine Series

The HEARS survey responses of the TAMC 601 cohort and the unimmunized cohort, both of whom completed this survey between May 1 and August 31, 2000, were compared. Characterization of the two groups by gender, age, marital status, education, and total annual household income, as reported in the HEARS survey, is shown in Table 5.

Responses to each question were not statistically different between the two groups (Table 6). Because of the variability in demographic characteristics between the cohorts, relative risks were subsequently compared stratifying the survey results individually by gender, age, marital status, education, and total annual household income. The only association that was remarkable in this comparison of 26 indicators and 13 demographic variables (within five demographic categories) was that women in the immunized cohort were more likely to report that their general health was "poor or fair" compared with the unimmunized cohort (RR 4.4; 95% CI: 1.3–15.1). The report of poor or fair health occurred in six of

TABLE 6
Comparison of Responses to HEARS Survey Questions in AVA-immunized and Unimmunized TAMC Cohorts

HEARS Questions	Ratio Ratio	95% CI
General health as "Very Good to Excellent"	0.92	0.86–1.00
General health described as "Good"	1.30	0.98–1.72
General health described as "Poor to Fair"	1.58	0.67–3.71
Diagnosed with "Chronic Headaches"	1.21	0.77–1.90
Diagnosed with "Neurologic Disease"	1.05	0.36–3.04
Diagnosed with "Asthma"	1.12	0.69–1.83
Diagnosed with "Arthritis"	0.84	0.50–1.43
Diagnosed with "Muscle, Joint, or Back Problems"	1.00	0.76–1.33
Diagnosed with "Depression"	0.97	0.61–1.54
Mental health described as "Very Good to Excellent"	1.02	0.97–1.08
Mental health described as "Good"	0.78	0.52–1.18
Mental health described as "Poor to Fair"	1.40	0.58–3.39
Experience "Lots of Stress" past 12 months	1.01	0.88–1.17
Experience "Moderate Stress" past 12 months	0.99	0.86–1.13
Experience "Little to No Stress" past 12 months	1.31	1.00–1.71
Saw mental health professional past 12 months	1.15	0.78–1.71
Had serious personal or emotional problems past 12 months	1.11	0.77–1.60
Often bothered by feeling down, depressed, or hopeless	1.36	0.69–2.70
Sometimes bothered by feeling down, depressed, or hopeless	1.00	0.67–1.50
Seldom or "Never" bothered by feeling down, depressed, or hopeless	0.99	0.93–1.04
Often bothered by little interest or pleasure in doing things	1.37	0.69–2.71
Sometimes bothered by little interest or pleasure in doing things	1.40	0.90–2.18
Seldom or "Never" bothered by little interest or pleasure in doing things"	0.95	0.90–1.01
Not Satisfied with my life	1.47	0.75–2.87
Somewhat Satisfied with my life	1.33	0.98–1.82
"Mostly" or "Totally" satisfied with my life	0.93	0.86–1.00

91 women (6.6%) in the immunized cohort compared with four of 264 women (1.5%) in the non-immunized cohort. Otherwise, there were no notable trends or associations.

Cohort Study of Outpatient Health Care Visits and Hospitalizations

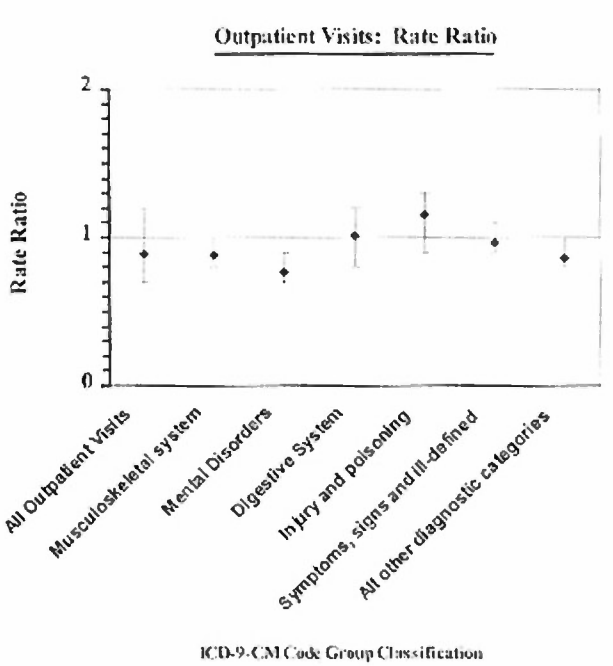
Rate ratios comparing rates of outpatient visits and hospitalizations in the period before the first anthrax immunization (or no immunization) with the rate of outpatient visits and hospitalizations in the period after the first immunization, both unadjusted as well as adjusted for age and gender are shown in Fig. 2. The rate ratio for outpatient visits for mental health was lower in the immunized versus unimmunized cohorts and was statistically significant (RR: 0.76; 95% CI: 0.7–0.9, unadjusted; RR: 0.82; 95% CI: 0.8–0.9, adjusted). Otherwise, rate ratios were unremarkable.

We also compared rates of leaving active Army service between the TAMC 601 cohort and the TAMC unimmunized cohort (group 3, methods) and noted that rates of discharge were 1.7 times higher in the non-immunized control group compared to the TAMC 601 cohort. Numerators for these rates were defined as soldiers who voluntarily left the active Army, were separated due to medical or administrative causes, or retired.

Discussion

Assessments of four distinct health care outcomes were used to characterize potential adverse events in 601 consecutive healthcare personnel immunized with AVA at TAMC. Short-term outcomes were assessed using two survey questionnaires of self-reported events that occurred after AVA immunization and VAERS reports of more serious events temporally associated with AVA immunization. Longer-term outcomes of up to 2 years were assessed by comparing reported health information from a standardized health appraisal instrument as well as rates of outpatient visits and hospitalizations in immunized and non-immunized soldiers.

Localized reactions, including erythema, local tenderness, subcutaneous nodules, and localized itching, were commonly reported and occurred more often in women than men. This is consistent with other surveys that evaluated events by gender.[26–29] Systemic events, such as fatigue, headache, and arthralgias, were less commonly reported than localized events, consistent with other studies,[11,26,27,30] and were reported more often in women than men.[27,30] Events occasionally resulted in brief limitation of activities, which also occurred more commonly in women than men. The Institute of Medicine[28] concluded that the types of local and systemic reactions associated with AVA and the rates at which they were observed are comparable to those observed with other vaccines regularly administered to adults, such as diphtheria and tetanus



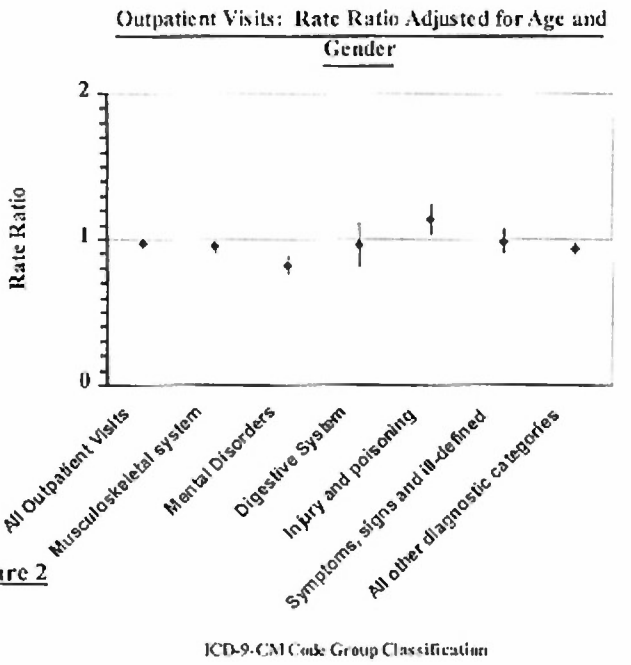
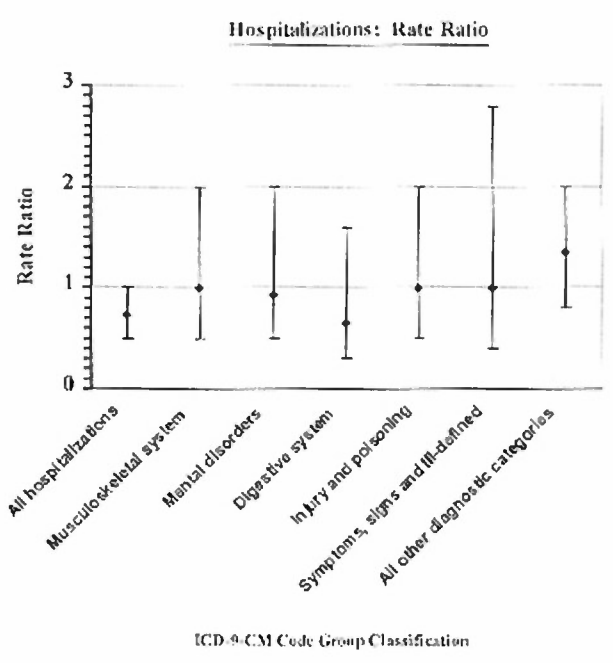


Figure 2



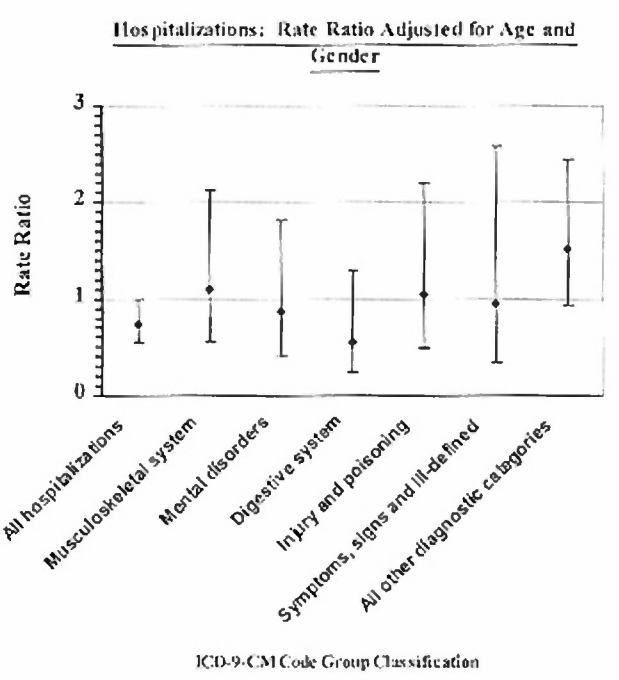


Fig. 2. Rate ratios of outpatient visits and hospitalizations for AVA-immunized and unimmunized TAMC cohorts

toxoids and influenza vaccines.[28,31,32] Most vaccine studies have not compared post-immunization events by gender, but those that have generally found higher rates of local reactions among women with similar rates of systemic reactions in both sexes.[28,31] The factors accounting for sex differences are not known.

The five cases reported to the VAERS did not reveal any trends either by themselves or in the broader scope of the VAERS.[29] These individuals were medically exempted from further immunization, although the 32-year-old soldier with the history of sarcoidosis asked to be given the vaccine again and had no further significant side effects. Only the 38-year-old soldier with the large local reaction had an event that could be unequivocally attributed to immunization. The others had varying degrees of associated uncertainty and possible attribution to causes unrelated to anthrax vaccine. The possibility of complex interactions is also present. For example, the 23-year-old soldier with evidence of an

inflammatory demyelinating disease may have had latent multiple sclerosis before immunization, but immunization may have facilitated unmasking the symptoms. All five cases were reported to the VAERS because the goal of the VAERS is to cast a wide net and capture any significant sentinel events that might be attributable to the anthrax vaccine.[21,28] These events can then be evaluated epidemiologically using population databases, such as DMSS, to determine the strength of association for these events in immunized and unimmunized cohorts and investigate a potential causal relationship.[16,28] At present, only localized events reported to VAERS are known to be causally related to immunization with AVA.[16,28]

Self-reported health and wellness indicators using the HEARS health risk appraisal instrument enabled us to compare another dimension of health outcomes between immunized and non-immunized soldiers. Evaluation of 26 key health indicators did not reveal any significant differences between immunized and non-immunized cohorts. Availability of information on age, gender, education, and family income allowed us to investigate demographic subpopulations to determine if we could discern any significant difference in reported health between the immunized and non-immunized cohorts. The only statistically significant association in this entire analysis, a report of poor or fair health occurred in six of 91 women (6.6%) in the immunized cohort compared with four of 264 women (1.5%) in the non-immunized cohort, may be due to a statistical anomaly with multiple comparisons using $P < 0.05$ as a cutoff. The association, on the other hand, may be valid, with immunization a confounder or surrogate for deployability that is considered a greater challenge for women than men, particularly those who have children.

We compared rates of outpatient visits and hospitalizations between immunized and non-immunized soldiers who were stationed at TAMC on 1 October 1998 using ICD-9 CM diagnostic groups. In our analysis, rate ratios for categories of outpatient visits and hospitalizations for immunized versus non-immunized TAMC soldier cohorts were unremarkable, even after adjusting for age and gender. Comparing diagnostic categories, only outpatient mental health visits were statistically significant ($P < 0.05$) with rates lower in the immunized cohort.

The AMSA evaluates rates of outpatient visits and hospitalizations by ICD-9 CM diagnostic groups periodically to identify any population-based trends in vaccine-related events. Events identified by VAERS or excess of outpatient visits or hospitalizations in a relevant diagnostic category would prompt an epidemiological analysis of specific disease entities using a population database, for example, the DMSS and Naval Health Research Center (NHRC) databases.[28,33] To date, no significant elevations have been identified, after adjusting for multiple comparisons.

The use of four distinct study designs in this analysis helped to balance limitations of each, while contributing their own inherent strengths. Active surveillance was used in evaluation of events occurring after immunization, which may account for higher rates of reported events than studies using passive surveillance.[11,27,28,34] Surveillance covered the entire series of six immunizations in contrast to other population-based studies, but routine changeover in personnel in the active duty Army contributed significantly to dropout rates. A comparison of rates for soldiers leaving active Army service in this cohort indicated that immunized soldiers were much less likely to leave than unimmunized soldiers.

The surveys lacked a control group because a placebo group was considered unethical for individuals needing AVA to protect them from enemy use of weaponized anthrax. This could account in part for higher rates of reported side effects in surveys[26,28] compared with the only controlled trial done to evaluate anthrax vaccine side-effects.[11] Individuals' reporting of events are subject to observational bias, as well as misinterpretation of the questionnaire. Muscle aches on the first questionnaire were designed to identify systemic complaints of myalgia, yet we learned well into the study that these were almost always interpreted as a localized reaction by those surveyed. The absence of a control group and biases associated with patient self-reports does not enable us to accurately quantify the attributable rate of adverse events. Although sensitivity is high for detecting acute events after immunization, particularly any serious ones, specificity is low due to misattribution of events to anthrax immunization. Nonetheless, surveys are useful for identifying trends and potentially serious, acute adverse events.

The VAERS analysis facilitated identification of potentially serious sentinel events, which could subsequently be evaluated using large population databases like DMSS. By itself, VAERS has limited utility due to concerns associated with variability of reporting, determination of significance, and interpreting whether events are related to the anthrax vaccine.[28] Only the report of a large localized reaction could be definitively attributed to AVA-immunization, and this event resolved without intervention.

The two-arm cohort study of reported health and wellness using a standardized health risk appraisal instrument was particularly valuable because the data were nested and were not biased by knowledge of its potential use in this study by survey recipients. The use of a control group, as well as the ability to stratify using numerous relevant demographic variables, was an additional strength. Use of multiple comparisons, however, can reduce the level of specificity for detecting a statisti-

cally significant association, unless the P value is reduced. A potential weakness, characteristic of this type of survey, relates to the validity of responses provided by recipients and their uniformity in interpreting questions. This would be minimized if non-differential bias between cases and controls occurred.

The three-arm cohort study of outpatient visits and hospitalizations benefits from having a reasonable control group that can be adjusted for age and gender. Bias due to the healthy worker effect is potentially present. Availability of a relevant control group counters the problem noted using surveys that lack a control group in assessing attribution of adverse vaccine events resulting in outpatient visits and hospitalizations. Diagnostic categories and not individual diagnoses could be evaluated because of the statistical requirements with sample size. DMSS is currently using larger populations to evaluate both disease categories and specific diseases.[28,35] Analysis of outpatient visits and hospitalizations would not accurately detect mild adverse events, although this is balanced by our utilization of post-immunization surveys.

It is important to study effects of AVA-immunization in other groups, as has been done,[11,26,28–30,36] because of inherent uncertainties of generalizing reports from medical personnel to other population groups. A hospital staff cohort may display a potentially greater sensitivity for detecting post-immunization events, interpret events differently than the general public, has different occupational exposures, and has greater access to health care. Based on the aggregate analysis of studies there is no indication of serious adverse health effects at present.

A recent pilot study showed that intramuscular administration of AVA eliminated most of the injection site reactions noted with this vaccine. In addition, two doses of AVA administered 4 weeks apart were as immunogenic as three doses over 4 weeks at peak.[27] The CDC is currently conducting a large pivotal study to confirm these results. Intramuscular administration and fewer doses of AVA, if shown to be safe and effective in this trial, would only improve the benefit/risk ratio.

The findings of this study support the relative reactogenicity of AVA immunization but do not reveal any serious adverse events or effects on health. This is consistent with other published studies.[15,28] This strongly supports a benefit/risk ratio in favor of using AVA for DOD service members, particularly those deployed to high threat areas. The set of studies reported here identified no rationale for delaying protection of service members deploying to high risk areas who face the threat of aerosolized anthrax.

References

1. Pile JC, Malone JD, Eitzen EM, et al. Anthrax as a potential biological warfare agent. *Arch Intern Med.* 1998;158:429–434.
2. Zilinskas RA. Iraq's biological weapons: the past as future? *JAMA.* 1997;278:418–424.
3. Inglesby TV, Henderson DA, Bartlett JG, et al. Anthrax as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA.* 1999;28118:1735–1745.
4. Mazzuchi JF, Claypool RG, Hyams KC, et al. Protecting the health of US military forces: a national obligation. *Aviat Space Environ Med.* 2000;713:260–265.
5. Kortepeter MG, Parker GW. Bioterrorism: implications for the clinical microbiologist. *Clin Microbiol Rev.* 2001;14:364–381.
6. Miller J. Nuclear Anxieties in a New World. *New York Times* (Travel). February 5, 2000.
7. Cole LA. The specter of biological weapons. *Sci Am.* 1996;Dec:60–65.
8. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979. *Science.* 1994;2665188:1202–1208.
9. Davis CJ: Nuclear blindness: an overview of the biological weapons programs of the former Soviet Union and Iraq. *Emerg Infect Dis.* 1999;5:509–512.
10. Centers for Disease Control and Prevention. Investigation of bioterrorism-related anthrax—Connecticut, 2001. *MMWR.* 2001;50:1077–1079.
11. Brachman PS, Gold H, Plotkin SA, et al. Field evaluation of a human anthrax vaccine. *Am J Public Health.* 1962;52:432–445.
12. Brachman PS, Kaufmann AF, Dalldorf FG. Industrial inhalation anthrax. *Bact Rev.* 1966;30:646–659.
13. Food and Drug Administration. Biological products: bacterial vaccines and toxoids. Implementation of efficacy review. *Fed Reg.* 1985;50:51002–51117.
14. Demicheli V, Rivetti D, Deeks JJ, et al. The effectiveness and safety of vaccines against human anthrax: a systematic review. *Vaccine.* 1998;16:880–884.
15. Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States. *MMWR.* 2000;49:1–20.
16. Sever JL, Brenner AL, Gale AD, et al. Safety of anthrax vaccine: a review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiol. Drug Safety.* 2002;11:189–202.
17. Garrett L. A healthy shot of distrust/ military's disclosures, decree on anthrax vaccine sparks criticism. *Newsday* (Health and Discovery). May 4, 1999:C8.
18. United States Army Regulation 40–562, Navy Bureau of Medicine & Surgery Instruction 6230.15, Air Force Joint Instruction 48-110, CGCIM. *Immunizations & Chemoprophylaxis.* Washington, DC, November 1. 1995.
19. BioPort Corporation product labeling. Anthrax vaccine adsorbed., Lansing, Michigan, January 31, 2002.
20. Title 32 Code of Federal Regulations, section 219.
21. Singleton JA, Lloyd JC, Mootrey GT, et al. An overview of the vaccine adverse event reporting system (VAERS) as a surveillance system. VAERS Working Group. *Vaccine.* 1999;1722:2908–2917.
22. Grayson K, Brustrom JE. Health survey reliability in an active duty population. *Mil Med.* 2001;166:632–636.
23. Joseph SC. Policy for TRICARE Health Enrollment Assessment Review (HEAR) survey. Memorandum from Assistant Secretary of Defense Health Affairs through the Surgeon Generals of the Army, Navy, and Air Force to TRICARE Lead Agents. Health Affairs Policy 97–003.
24. Brundage JF, Kohlhase KF, Rubertone MV. Hospitalizations for all causes of US military service members in relation to participation in Operations Joint Endeavor and Joint Guard, Bosnia-Herze-

govina, January 1995 to December 1997. *Mil Med.* 2000;1657:505–511.

5. SAS Institute Inc. *SAS Language Reference.* Version 6, 1st ed. Cary, NC: SAS Institute Inc.; 1990.
6. Gunzenhauser JD, Cook JE, Parker ME, et al. Acute side effects of anthrax vaccine in ROTC cadets participating in advanced camp, Fort Lewis, 2000. *Med Surveillance Monthly Rep.* 2001; 7:9–14.
7. Pittman PR, Kim-Ahn G, Pifat DY, et al. Anthrax vaccine: safety and immunogenicity of a dose-reduction, route comparison study in humans. *Vaccine.* 2002;20: 1412–1420.
8. Institute of Medicine Committee to Assess the Safety and Efficacy of the Anthrax Vaccine. *The Anthrax Vaccine: Is It Safe? Does It Work?* Washington, DC: National Academy Press; 2002.
9. Centers for Disease Control and Prevention. Surveillance for adverse events associated with anthrax vaccination—US Department of Defense, 1998–2000. *MMWR.* 2000;49:341–345.
30. Pittman PR, Gibbs PH, Cannon TL, et al. Anthrax vaccine: short-term safety experience in humans. *Vaccine.* 2001;20:972–978.
31. Treanor JJ. Adverse reactions following vaccination of adults. Commissioned paper. Committee to Assess the Safety and Efficacy of the Anthrax Vaccine, Institute of Medicine, Washington, DC; 2002.
32. Grabenstein JD. *ImmunoFacts: Vaccines & Immunologic Drugs,* 27th ed. St. Louis, MO: Facts and Comparisons, Inc.; August 2002.
33. Sato PA, Reed RJ, Smith TC, et al. DOD-wide medical surveillance for potential long-term adverse events associated with anthrax immunizations: hospitalizations. *Vaccine.* 2002;20:2369–2375.
34. Centers for Disease Control and Prevention. Application and report on manufacture of anthrax protective antigen, aluminum hydroxide adsorbed (DBS-IND 180). Observational study. Atlanta, GA: Centers for Disease Control and Prevention;1967–1971.
35. Sato PA, Reed RJ, Smith TC, et al. Monitoring anthrax vaccine safety in U. S. military service members on active duty: surveillance of 1998 hospitalizations in temporal association with anthrax immunization. *Vaccine.* 2002;20:2369–2374.
36. Rehme PA, Williams R, Grabenstein JD. Ambulatory medical visits among anthrax vaccinated and unvaccinated personnel after return from southwest Asia. *Mil Med.* 2002;167:205–210.